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**UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

MARZI, Mauro et al. Atty. Ref.: 2818-225; Confirmation No. 2529

Appl. No. 10/511,724 TC/A.U. 1625

Filed: October 19, 2004 Examiner: Aulakh

For: CAMPTOTHECINS WITH A MODIFIED LACTONE RING

\* \* \* \* \*

March 15, 2006

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**SUBMISSION OF TRANSLATION OF PRIORITY APPLICATION**

Attached is a certified English translation of Italian application Serial No.  
RM2002A000305 filed May 21, 2002.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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**MINISTRY OF THE Productive Activity**

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Authentication of the copy of the documents relating to the patent application for industrial invention n° RM2002A000305.

It is hereby declared that the attached copy is a true copy of the original documents filed with the above-identified patent application, the data of which are given in the enclosed official filing certificate.

Rome, June 20, 2003

**The Dirigent**  
signed  
Dr. Potito Galloppo

**TO THE MINISTRY OF INDUSTRY, COMMERCE AND OF HANDICRAFTS**

**Central Patent Office - ROME**

**FORM A** duty stamp

**Patent application for Industrial Invention, late filing of documents and early disclosure to the public**

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Residence: Rome RM code:

2) Name: ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI DEI TUMORI

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**C. ELECTED DOMICILE:**

STREET: n° CITY: ZIP CODE (district)

**D. TITLE** proposed class (sect./cl./subcl.)

"Camptothecins with a modified lactone ring".

Early disclosure to the public: YES • NO •

**E. DESIGNATED INVENTORS:**

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(3) PENCO Sergio

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**F. PRIORITY**

Country or Organisation: NONE Type of Priority Filing N° Filing Date

Enclosures (Y/Will Follow)

**G. RECOGNIZED DEPOSITORY AUTHORITY, FOR THE DEPOSIT OF MICROORGANISMS, name**

**H. SPECIAL REMARKS:**

**ENCLOSED DOCUMENTS**

Quantity

Doc. 1) 2 Prov(isional) N° of pags 41 Specification with abstract and claims.  
Doc. 2) 0 Prov. N° of tables Drawings

Doc. 3) 2 Will follow Power of attorney  
Doc. 4) 0 Will follow Designation of inventor  
Doc. 5) 0 Will follow Priority document with Italian translation.  
Doc. 6) 0 Will follow Authorization or deed of assignment  
Doc. 7) 0 Complete applicant's name.  
8) Receipt of Payment, Total Euro Two Hundred Nine Thousand/80  
**FILED ON:** 31/05/2002 **Applicant's signature:** Marco Spadaro

A Certified Copy Of The Present Document Is Requested YES/NO Yes

**PROVINCIAL OFFICE OF INDUSTRY COMMERCE AND HANDICRAFTS**  
**ROME**

Code 58

**Filing Certificate:** Application N° RM2002A000305 Reg. A

In the year two thousand and two, on the thirtyfirst day of the month of May the above-mentioned applicant(s) has (have) submitted to the undersigned the present application, accompanied by n° 01 additional sheets for the granting of the above patent.

**1. Various Remarks By The Recording Officer:**

**The Depositing Employee**

Signed

**The Recording Officer**

Signed (Giuseppe Tafuri)

**Additional sheet to Form A**

Continuation sheet n° 1 of total n° 1

Application n° RM2002A000305

Reg. A

**A. APPLICANT(S):**

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**F. PRIORITY**

Country or Organisation	Type of Priority	Filing Number	Filing Date	Encls
Y/Will Follow				

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**Applicant's signature:**

Dr. Marco Spadaro

**Abstract Of Invention With Main Drawing, Description And Claim**

**Filing Number:** RM2002A000305

**Filing date:** 31.05.2002

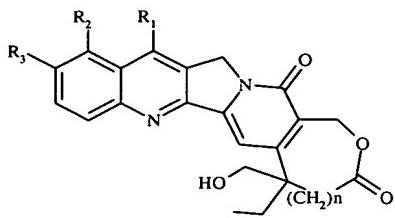
**Date of Grant:**

**D. TITLE:**

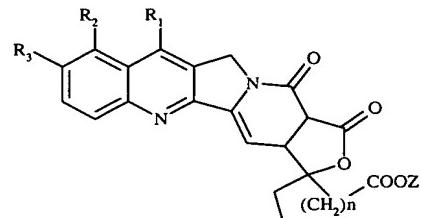
"Camptothecins with a modified lactone ring".

**L. ABSTRACT:**

Compounds of formula (I) or (II) are described:



(I)



(II)

wherein the groups are as defined in the description here below, the racemic mixtures, their individual enantiomers, their individual diastereoisomers, their mixtures, and their pharmaceutically acceptable salts. Said compounds are topoisomerase I inhibitors.

**M. MAIN DRAWING:**

**Description of the invention entitled:  
"Camptothecins with a modified lactone ring"**

in the name of: SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.  
ISTITUTO NAZIONALE PER LO STUDIO E CURA DEI TUMORI

nationality: Italian

with registered office in:

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The invention described herein relates to compounds useful as medicines, particularly derivatives of camptothecin with structural modifications of the lactone ring, to processes for their preparation, to their use as active agents endowed with topoisomerase I inhibiting activity and to pharmaceutical compositions containing them as active ingredients.

**Background of the invention**

Camptothecin is an alkaloid isolated by Wall *et al.* (*J. Am. Chem. Soc.* 88, 3888-3890 (1966)) for the first time from the tree *Camptotheca acuminata*, a plant native to China, belonging to the *Nyssaceae* family.

The molecule consists of a pentacyclic structure with a lactone in the E ring, which is essential for cytotoxicity.

For a review of the camptothecins and the problems relating to their use as medicines, as well as the resolution of a number of such problems, see European Patent EP 1044977, filed in the name of the applicant.

As regards the problem of the lactone ring, which is a portion of the molecule essential for the camptothecins to be able to exercise their pharmacological activity, one aspect which has yet to be fully resolved is the stability of the ring itself, which, in turn, is responsible for the half-life of the drug.

Patent application WO 97/00876, filed in the name of Societè de Conseils de

Recherches et d'Applications Scientifiques, and published on 09.01.1997, describes camptothecins in which the lactone ring has been modified from its original  $\alpha$ -hydroxylactone structure to a  $\beta$ -hydroxylactone structure (homocamptothecins), bringing the lactone cycle up from six to seven members. These compounds inhibit topoisomerase I DNA relaxation activity and are endowed with cytotoxic activity against several tumour lines. The  $\beta$ -hydroxylactone structure is defined as a lactone that involves the presence of a supplementary carbon atom between the carboxyl carbon atom and the carbon atom in  $\alpha$ -bearing the hydroxyl in the  $\alpha$ -hydroxylactone structure. To increase the stability of the lactone ring, the inventors suggest substituents on the supplementary carbon atom, and the substituents indicated are the lower alkyls together with the lower alkoxy, halogen or hydroxyl. In the patent application mentioned no evidence of improved stability of the lactone ring is provided. In a subsequent patent application, WO 98/28304, published on 02.07.1998, the same applicant describes further camptothecins with a  $\beta$ -hydroxylactone structure, where the hydroxyl group is functionalised with groups that are capable of restoring it *in vivo*, thus effectively furnishing prodrugs of the molecules described in the preceding patent application, and also resolving the problem of the severe side effects of products in the present state of the art. In this case, too, no experimental evidence is provided that the technical problem has been solved. In *J. Med. Chem.* 1998, Vol 41, No 27, 5410-5419, the same inventors as in the abovementioned patent applications indicate the lactone in position 7, therein described, as an instrument for increasing the stability of the lactone ring, and thus as a useful model for elaborating further camptothecin derivatives. See also *Bioorg. Med. Chem. Lett.* 9, (1999) 2599-2602; *Biochemistry* 1999, 38, 15556-15563; *Cancer Research* 59 2939-2943. Other modifications of homocamptothecin on the A and B rings are described in WO 00/61146, University of Pittsburgh et al., published on 19.10.2000, and in *J. Med. Chem.* 1999, 42, 3018-3022 for the so-called "homosilatecans", which are potent, stable topoisomerase I inhibitors. Homocamptothecins with further modifications are described in *J. Med. Chem.* 2000, 43, 2285-2289, *Anti-cancer Drug Design* (2001), 12, 9-19, where the anticancer activity is increased thanks to the fluoridation of the A ring. See also *Anti-cancer Drug Design* (2001), 16, 27-36, for the substitution with chlorine in position 12.

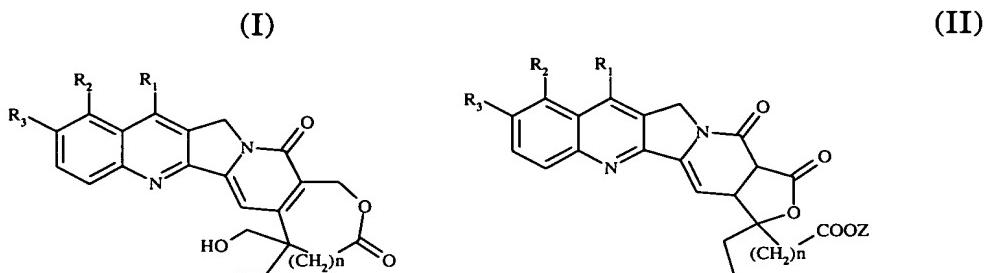
The problem of the hydrosolubility of the homocamptothecins is addressed in US 6,291,676, University of Kentucky, published on 18.09.2001 with various substitutions of the (poly)alkylamine type in position 7.

However much in the design of new drugs various problems are encountered of a physicochemical nature, such as the stability of the molecule in plasma or its hydrosolubility for formulatory purposes, there is a constant search for a better therapeutic index.

## Summary of the invention

It has now surprisingly been found that substituted 7-oxime camptothecins, with a modified lactone ring, are endowed with substantial anticancer activity and are stable in plasma. These compounds have a better therapeutic index.

The subjects of the invention described herein are therefore compounds of general formula (I) and (II):



where:

R<sub>1</sub> is hydrogen or a -C(R<sub>5</sub>)=N-O-R<sub>4</sub> group, in which R<sub>4</sub> is hydrogen or a straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkenyl group, or a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, or a straight or branched (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a C<sub>6</sub>-C<sub>14</sub> aryl group, or a straight or branched (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a heterocyclic group or a straight or branched heterocycle - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, said heterocyclic group containing at least one heteroatom selected from an atom of nitrogen, possibly substituted with an (C<sub>1</sub>-C<sub>5</sub>) alkyl group, and/or an atom of oxygen and/or of sulphur; said alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aryl-alkyl, heterocyclic or heterocycle-alkyl groups may possibly be substituted with one or more groups chosen from: halogen, hydroxy, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, phenyl, cyano, nitro, and -NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, which may be the same or different, are hydrogen, straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl, the -COOH group or one of its pharmaceutically acceptable esters; or the -CONR<sub>8</sub>R<sub>9</sub> group, where R<sub>8</sub> and R<sub>9</sub>, which may be the same or different, are hydrogen, straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl; or

R<sub>4</sub> is a (C<sub>6</sub>-C<sub>10</sub>) aroyl or (C<sub>6</sub>-C<sub>10</sub>) arylsulphonyl residue, possibly substituted with one or more groups selected from: halogen, hydroxy, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl, straight or branched C<sub>1</sub>-C<sub>5</sub> alkoxy, phenyl, cyano, nitro, -NR<sub>10</sub>R<sub>11</sub>, where R<sub>10</sub> and R<sub>11</sub>, which may be the same or different, are hydrogen, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl; or:

R<sub>4</sub> is a polyaminoalkyl residue; or

R<sub>4</sub> is a glycosyl residue;

R<sub>5</sub> is hydrogen, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl, straight or branched C<sub>1</sub>-C<sub>5</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, straight or branched (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl, C<sub>6</sub>-C<sub>14</sub> aryl, straight or branched (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl;

R<sub>2</sub> and R<sub>3</sub>, which may be the same or different, are hydrogen, oxhydryl, straight or

branched C<sub>1</sub>-C<sub>5</sub> alkoxy;

n = 1 or 2,

Z is selected from hydrogen, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

the N<sub>1</sub>-oxides, the racemic mixtures, their individual enantiomers, their individual diastereoisomers, their mixtures, and their pharmaceutically acceptable salts, on condition that, in formula (I), R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> cannot be simultaneously hydrogen.

The present invention includes the use of compounds of the above-mentioned formulae (I) and (II) as active ingredients for medicines, particularly for medicines which are useful as topoisomerase I inhibitors. Among the therapeutic applications deriving from topoisomerase I inhibition we should mention the treatment of tumours and parasitic or viral infections.

The present invention includes pharmaceutical compositions containing compounds of formula (I) and/or formula (II) as active ingredients, in mixtures with pharmaceutically acceptable vehicles and excipients.

The present invention also includes the processes for the preparation of compositions of formula (I) and (II), and the key intermediate products.

#### **Detailed description of the invention**

Within the framework of the present invention, examples of the straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl group, are understood to include methyl, ethyl, propyl, butyl, pentyl and their possible isomers, such as, for example, isopropyl, isobutyl, and ter-butyl.

Examples of the branched or straight C<sub>1</sub>-C<sub>5</sub> alkenyl group are methyldene, ethyldene, vinyl, allyl, propargyl, butylene, and pentylene, where the double carbon-carbon bond may be situated in the various possible positions of the alkylene ring, which can also be branched in the context of the isomery allowed.

Examples of the C<sub>3</sub>-C<sub>10</sub> cycloalkyl group are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and polycyclic groups, such as, for example, adamantyl.

Examples of the straight or branched (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group are cyclopropylmethyl, 2-cyclopropylethyl, 1-cyclopropylethyl, 3-cyclopropylpropyl, 2-cyclopropylpropyl, 1-cyclopropylpropyl, cyclobutylmethyl, 2-cyclobutylethyl, 1-cyclobutylethyl, 3-cyclobutylpropyl, 2-cyclobutylpropyl, 1-cyclobutylpropyl, cyclohexylmethyl, 2-cyclohexylethyl, 1-cyclohexylethyl, 3-cyclohexylpropyl, 2-cyclohexylpropyl, 1-cyclohexylpropyl, 5-cyclohexylpentyl, 3-cyclohexylpentyl, 3-methyl-2-cyclohexylbutyl, 1-adamantylethyl, 2-adamantylethyl, adamantlylmethyl.

Examples of the straight or branched (C<sub>6</sub>-C<sub>14</sub>) aryl or (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group are phenyl, 1- or 2-naphthyl, anthracenyl, benzyl, 2-phenylethyl 1-phenylethyl, 3-phenylpropyl, 2-anthracenylpropyl, 1-anthracenylpropyl, naphthylmethyl, 2-naphthylethyl, 1-naphthylethyl, 3-naphthyl-propyl, 2-naphthylpropyl, 1-naphthylpropyl, cyclohexylmethyl,

5-phenylpentyl, 3-phenylpentyl, 3-methyl-2-phenylbutyl.

Examples of the straight or branched heterocyclic or heterocycle - (C<sub>1</sub>-C<sub>5</sub>) alkyl group are thienyl, quinolyl, pyridyl, N-methylpiperidinyl, 5-tetrazolyl, 2-(4,5-dihydroxazolyl), 1,2,4-oxadiazolidin-3-yl-5-one, purine and pyrimidine bases, e.g. uracyl, possibly substituted as indicated in the general definitions above.

Examples of the (C<sub>6</sub>-C<sub>10</sub>) aroyl groups are benzoyl and naphthoyl.

Examples of the (C<sub>6</sub>-C<sub>10</sub>) arylsulphonyl groups are tosyl and benzoysulphonyl.

What is meant by halogen is fluorine, chlorine, bromine and iodine.

Examples of substituted groups are pentafluorophenyl, 4-phenylbenzyl, 2,4-difluorobenzyl, 4-aminobutyl, 4-hydroxybutyl, dimethylaminoethyl, p-nitrobenzoyl, p-cyanobenzoyl.

An example of the polyaminoalkyl residue is -(CH<sub>2</sub>)<sub>m</sub>-NR<sub>12</sub>-(CH<sub>2</sub>)<sub>p</sub>-NR<sub>13</sub>-(CH<sub>2</sub>)<sub>q</sub>-NH<sub>2</sub>, where m, p and q are whole numbers from 2 to 6 inclusive and R<sub>12</sub> and R<sub>13</sub> are a straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl group, for example 4-aminobutyl-2-aminoethyl, 3-amino-propyl-4-aminobutyl, 3-aminopropyl-4-aminobutyl-3-aminopropyle.

Examples of the glycosyl residue are 6-D-galactosyl and 6-D-glucosyl.

Examples of pharmaceutically acceptable salts are, in the case of atoms of nitrogen of a basic nature, salts with pharmaceutically acceptable acids, both inorganic and organic, such as, for example, hydrochloric acid, sulphuric acid, acetic acid, or, in the case of an acid group, such as carboxyl, salts with both inorganic and organic pharmaceutically acceptable bases, such as, for example, alkaline and alkaline-terrous hydroxides, ammonium hydroxide, and amines, including heterocyclic amines.

One initial group of preferred compounds consists of formula (I) compounds in which the lactone ring is 7- or 8-membered, particularly 7-membered.

A second group of preferred compounds consists of formula (II) compounds in which the lactone ring is 5-membered.

In the context of the above-mentioned two preferred groups, those preferred are the formula (I) compounds, in which R<sub>4</sub> is other than hydrogen, and particularly a straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkenyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl, or (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a straight or branched C<sub>6</sub>-C<sub>14</sub> aryl, or (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a straight or branched heterocyclic or heterocycle - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, said heterocyclic group containing at least one heteroatom selected from an atom of nitrogen, possibly substituted with a (C<sub>1</sub>-C<sub>5</sub>) alkyl group, and/or of oxygen and/or of sulphur; said alkyl, alkenyl, cycloalkyl, aryl, aryl-alkyl, heterocycle or heterocyle-alkyl groups, may be substituted with one or more groups selected from: halogen, hydroxy, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, phenyl, cyano, nitro, -NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, which may be the same or different, are straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl; the -COOH group or one of its pharmaceutically

acceptable esters; or the  $-\text{CONR}_8\text{R}_9$  group, where  $\text{R}_8$  and  $\text{R}_9$ , which may be the same or different, are hydrogen, straight or branched ( $\text{C}_1\text{-C}_5$ ) alkyl, according to the definitions outlined above as examples.

An initial group of particularly preferred compounds consists of formula (I) compounds, with a 7-membered lactone ring, and, among these, particularly:

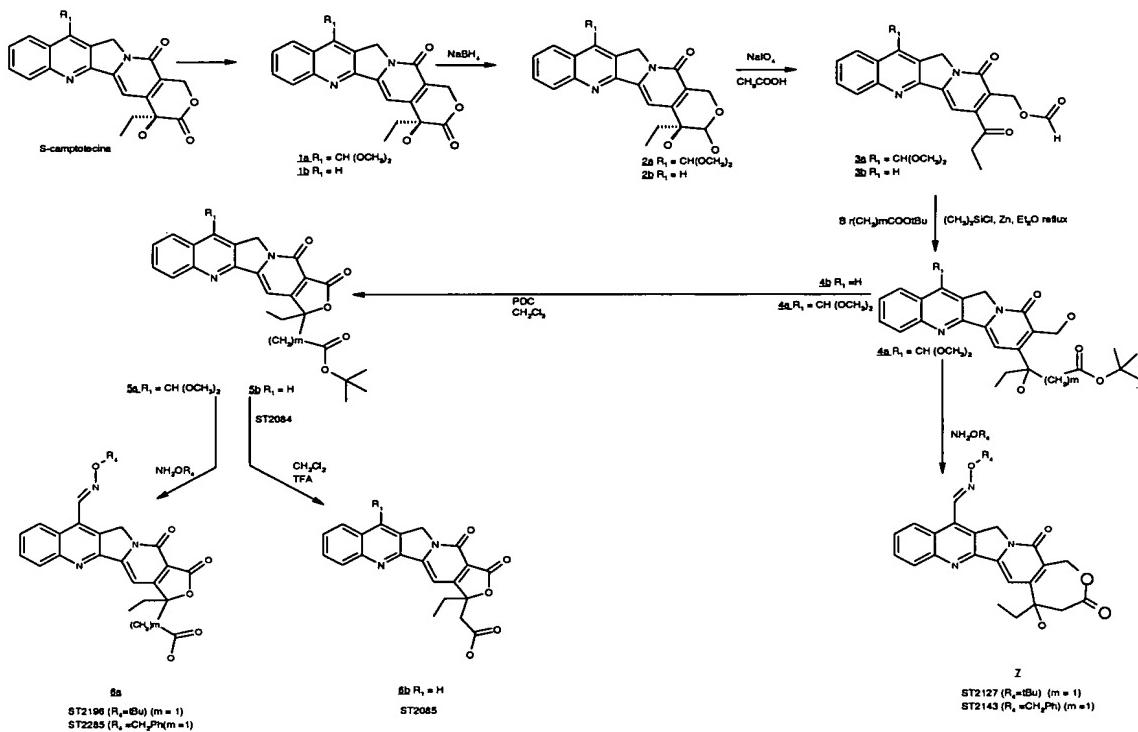
R,S-7-methoxyiminomethyl-homocamptothecin;  
R,S-7-ethoxyiminomethyl-homocamptothecin;  
R,S-7-isopropoxyiminomethyl-homocamptothecin;  
R,S-7-(2-methylbutoxy)iminomethyl-homocamptothecin;  
R,S-7-(1-t-butoxy)iminomethyl-homocamptothecin (ST2127);  
R,S-7-(4-hydroxybutoxy)iminomethyl-homocamptothecin;  
R,S-7-triphenylmethoxyiminomethyl-homocamptothecin;  
R,S-7-carboxymethoxyiminomethyl-homocamptothecin;  
R,S-7-aminoethoxyiminomethyl-homocamptothecin;  
R,S-7-(N,N-dimethylaminoetoxy)iminomethyl-homo- camptothecin;  
R,S-7-allyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclohexyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclohexylmethoxyiminomethyl-homocampto-thecin;  
R,S-7-cyclooctyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclooctylmethoxyiminomethyl-homocamptothecin;  
R,S-7-benzyloxyiminomethyl-homocamptothecin (ST2143);  
R,S-7-(benzyloxy)iminophenylmethyl-homocamptothecin;  
R,S-7-(1-benzyloxy)iminoethyl-homocamptothecin;  
R,S-7-(1-t-butoxy)iminoethyl-homocamptothecin;  
R,S-7-p-nitrobenzyloxyiminomethyl-homocamptothecin;  
R,S-7-p-metilbenzyloxyiminomethyl-homocamptothecin;  
R,S-7-pentafluorobenzyloxyiminomethyl-homocampto-theclin;  
R,S-7-p-phenylbenzyloxyiminomethyl-homocampto-theclin;  
R,S-7-(2,4-difluorobenzylmethoxy)iminomethyl-homo- camptothecin;  
R,S-7-(4-t-butylphenylmethoxy)iminomethyl-homo-camptothecin;  
R,S-7-(1-adamantyloxy)iminomethyl-homocamptothecin;  
R,S-7-(1-adamantylmethoxy)iminomethyl-homocampto-theclin;  
R,S-7-(2-naphthalenyloxy)iminomethyl-homocampto-theclin;  
R,S-7-(9-anthracyl methoxy)iminomethyl-homo-camptothecin;  
R,S-7-(6-uracyl)methoxyiminomethyl-homocamptothecin;  
R,S-7-(4-pyridil)methoxyiminomethyl-homocamptothecin;  
R,S-7-(2-thienyl)methoxyiminomethyl-homocampto-theclin;

R,S-7-[(N-methyl)-3-piperidinyl]methoxyiminomethyl-homocamptothecin;  
R,S-7-hydroxyiminophenylmethyl-homocamptothecin.

Among these compounds, those most preferred are R,S-7-(1-t-butoxy)iminomethyl-homocamptothecin (ST2127) and R,S-7-benzyloxyiminomethyl-homocamptothecin (ST2143).

A second group of particularly preferred compounds consists of formula (II) compounds, with a 5-membered lactone ring and with the same meanings of R<sub>1</sub> as in the preceding group.

Among these compounds, those which are most preferred are {10-[(E)-(tert-butoxyimino)methyl]-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-



b]quinonolin-3-yl}acetic acid (ST2196), (10-{(E)-[(benzyloxy)imino]methyl}-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid (ST2285) and (3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid (ST2085).

In a first preferred embodiment of the invention, compounds of general formula (I) are envisaged, where the lactone ring is 7- or 8-membered.

In a second preferred embodiment of the invention, compounds of general formula (II) are envisaged, where the lactone ring is 5-membered.

The formula (I) compounds can be prepared with the process described here below and exemplified for the preferred compounds according to the present invention.

It is quite obvious to the technician with ordinary experience in the field that the process scheme applies to all the compounds covered by formulae (I) and (II), since the method for obtaining the two classes of compounds with the 7/8-membered lactone ring, on the one hand, and the 5-membered ring, on the other, is fully described. The preparation of the various compounds covered by the two formulae differs in the substituent in position 7.

This preparation is described amply and completely in the above-mentioned EP 104977.

As regards the formula (I) and (II) compounds in which R<sub>1</sub> is hydrogen, the starting compound is camptothecin, possibly substituted in positions 8 and 9 according to the meanings of the R<sub>2</sub> and R<sub>3</sub> groups envisaged above.

In the case of formula (I) and (II) compounds in which R<sub>1</sub> is other than hydrogen, the functionalisation of position 7 to obtain the final compound cannot happen before the modification of the original lactone ring of camptothecin, both in the sense of its amplification to 7 or 8 members and in the sense of its restriction to 5 members. For this purpose, it has proved necessary to find a suitable intermediate product for the synthesis pathway envisaged. This key intermediate is 7-(dialkoxymethyl)camptothecin. This new compound is an additional subject of the present invention. Among these, the preferred compound is 7-(dimethoxymethyl)camptothecin. The camptothecin is reacted with the desired alcohol, which can also be used as a reaction medium, in the presence of a mineral acid, such as, for example, sulphuric acid, and a suitable oxidizing system, such as iron sulphate/oxygenated water, then a further oxidizing agent, such as manganese dioxide to obtain 7-(dialkoxymethyl)camptothecin.

Camptothecin, or its 7-(dialkoxymethyl)-derivative, are subjected to selective reduction of the carbonyl in position 19, to obtain the corresponding 19,20-dihydroxy derivative. The reduction is conducted in the presence of a reducing agent, for example, mixed hydrides of Al or B and exemplified in the scheme by sodium borohydride, from 1 to 10 equivalents in the presence of an alcoholic solvent for a period of time ranging from 1 to 16 h at a temperature ranging from ambient temperature to 50°C. The solvent is subsequently evaporated and the crude product is used in the subsequent step, where the E ring, in the form of the 19,20-dihydroxy derivative, is subjected to opening with from 1 to 10 equivalents of an oxidizing agent, such as, for example, periodate or lead acetate. The reaction is conveniently conducted in an organic solvent, such as, for example, toluene, methylene chloride or acetic acid, for a time period ranging from 1 to 24 h, at a temperature ranging from ambient temperature to 50°C. The solvent is removed in vacuo and the product is finally purified by chromatography or some other equivalent means. The intermediate product thus obtained is in turn dissolved in a suitable solvent medium, preferably a mixture of solvents, and then subjected to the well known Reformatsky

reaction, in which the  $\omega$ -bromocarboxylic acid is suitably selected as a function of the n value envisaged in formula (I) or (II). At this point, in the context of the embodiment of the present invention relating to formula (I) compounds, to the product of the Reformatsky reaction, dissolved in a suitable mixture of solvents, such as, for example, methylene chloride, acetic acid, and dimethyl formamide, possibly in the presence of an acid (for example, trifluoroacetic acid or a Lewis acid) and of a condensing agent (dicyclohexylcarbodiimide - DCC - or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) or a dehydrating agent (for example, sodium or magnesium sulphate, or molecular sieves), are added from 1 to 10 equivalents of a suitable hydroxylamine  $\text{NH}_2\text{OR}_4$ , also in the form of a salt, where  $\text{R}_4$  has the meanings described above for times ranging from 1 to 24 h, at a temperature ranging from ambient temperature to the boiling point of the solvent, to obtain the final formula (I) compound. The final product is isolated by removal of the solvent and final purification, for example, by chromatography. Alternatively, in the context of the second preferred embodiment of the invention, that is to say of formula (II) compounds in which the lactone ring is 5-membered, the product of the Reformatsky reaction, after being dissolved in a mixture of organic solvents, such as methylene chloride, acetic acid, and acetonitrile, is treated with from 1 to 10 equivalents of an oxidizing agent (for example, chromic acid, pyridinium dichromate - PDC - manganese oxide,  $\text{Na}_2\text{RuO}_4$ ) at a temperature ranging from 0°C to the boiling point of the solvent, for a time period ranging from 30 minutes to 24 h. The solvent is then removed in vacuo and the product purified by chromatography. The resulting compound is dissolved in a suitable organic solvent, such as, for example, methylene chloride) or an aqueous solvent and subjected to acid hydrolysis with an organic or inorganic acid, such as trifluoroacetic acid, hydrochloric acid, or perchloric acid) for a time period ranging from 1 to 24 h at a temperature ranging from 0°C to the boiling point of the solvent. The latter is then removed and the product isolated by crystallization. If desired, the product is finally reacted with the hydroxylamine  $\text{NH}_2\text{OR}_4$  as seen above. If formula (II) compounds, where Z is hydrogen, are desired, the compound obtained by the process described here above will be subjected to suitable treatment to release the carboxylic function according to conventional ester hydrolysis methods with which the experts in the field are fully familiar.

The reaction with the hydroxylamine  $\text{NH}_2\text{OR}_4$  is amply described in the above-mentioned patent EP 1044977, as is the preparation of possible N-oxides.

Pharmaceutically acceptable salts are obtained with conventional methods reported in the literature and do not require any further description.

The compounds described in the present invention are topoisomerase I inhibitors and therefore are useful as medicines, particularly for the treatment of diseases that benefit from the inhibition of said topoisomerase. In particular, the compounds according to

the present invention display antiproliferative activity and are therefore used on account of their therapeutic activity and possess physicochemical properties that make them suitable for formulation in pharmaceutical compositions.

The pharmaceutical compositions contain at least one formula (I) and/or formula (II) compound as an active ingredient, in an amount such as to produce a significant therapeutic effect. The compositions covered by the present invention are wholly conventional and are obtained with methods which are common practice in the pharmaceutical industry. According to the administration route opted for, the compositions will be in solid or liquid form, suitable for oral, parenteral, or intravenous administration. The compositions according to the present invention contain, along with the active ingredient, at least one pharmaceutically acceptable vehicle or excipient. Particularly useful may be formulation coadjuvants, such as, for example, solubilizers, dispersers, suspension agents and emulsifiers.

The formula (I) compounds can also be used in combination with other active ingredients, such as, for example, other anticancer drugs or other drugs with antiparasitic or antiviral activity, both in separate and in single dosage forms.

The compounds according to the present invention are useful as medicines with anticancer activity, for example, in lung cancers, such as non-microcytoma lung cancer, or in colorectal or prostate tumours or gliomas.

The cytotoxic activity of the compounds according to the present invention has been assayed in cell systems of human tumour cells, using the antiproliferative activity test as the method of evaluating the cytotoxic potential.

The cell line used is a non-microcytoma pulmonary adenocarcinoma called NCI H460, belonging to the NSCLC (non small cell lung cancer) class.

#### **Anticancer activity**

To evaluate the effect of the compounds according to the present invention, their cytotoxicity against the non-microcytoma lung cancer cell line (NCI-H460) was evaluated. Cells from the American Type Culture Collection (ATCC) were maintained in culture in RPMI 1640 (GIBCO) containing 10% foetal calf serum and gentamicin sulphate at a concentration of 50 µg/ml.

The cells were seeded in a volume of 250 µl in 96-well plates and incubated for 24 h at 37°C. The next day the study compounds were added at scalar concentrations from 1 µM to 0.004 µM, and the cells were incubated for another 2 h at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. The cells were washed 3 times, overturning the plates each time and adding PBS. 200 µl/well of RPMI 1640 medium containing 10% FCS were added and the plates were incubated at 37°C for a further 72 h. On day 5, the growth medium was removed by overturning the plates, and 200 µl/well of PBS and 50 µl of 80% cold TCA were

added. The plates were then incubated in ice for at least 1 h. The TCA was removed by overturning; the plates were washed 3 times by immersion in distilled water and dried first on blotting paper and then under a hot air jet. 200  $\mu$ l of 0.4% sulforodamine B in 1% acetic acid were added to all wells. The plates were incubated at ambient temperature for a further 30 minutes. The sulforodamine B was removed by overturning; the plates were washed by immersion 3 times in 1% acetic acid and then dried first on paper and then with a jet of hot air. 200  $\mu$ l of Tris base 10 mM were added to all wells and the plates were subjected to stirring for at least 20 minutes. The optical density was measured using a Multiskan spectrophotometer at 540 nm.

Table 1 presents the IC<sub>50</sub> values, that is to say the concentration capable of inhibiting 50% of cell survival, for each compound examined, processed using ALLFIT software.

TABLE 1

Product	NCI-H460 IC <sub>50</sub> ( $\mu$ M)
ST2084	>1
ST2085	>1
ST2127	0.026
ST2143	0.007
ST2196	>1
ST2285	>1

The following examples further illustrate the invention, referring to the scheme indicated above.

## PREPARATION 1

### Synthesis of 7-(dimethoxymethyl)camptothecin (ST2337)

To a suspension of 1.53 g (4.4 mmol) of camptothecin in 92 ml of methanol, cooled with an ice bath under stirring, were added slowly 9.2 ml of H<sub>2</sub>SO<sub>4</sub> 96%, keeping the temperature of the mixture below 50°C. The suspension thus obtained was heated to reflux temperature; on reaching 50°C, 46 mg of FeSO<sub>4</sub> · 7H<sub>2</sub>O were added and then 3 ml di H<sub>2</sub>O<sub>2</sub> 30% dropwise, keeping the reaction at reflux temperature. The reaction was stirred for 2 hours, checking for disappearance of the starting product by TLC. On completion of the reaction, the suspension was cooled to 25°C and 2.8 ml of MnO<sub>2</sub> were added; the mixture was stirred for 2 hours, checking for disappearance of the intermediate product by TLC. The suspension was then filtered through a layer of celite placed on a Gooch filter. The filtered solution was concentrated to 25 ml and then poured into a solution of NaHCO<sub>3</sub> in water so as to obtain a solution at pH 6. The precipitate was filtered and purified on a silica gel chromatography column (eluents: CH<sub>2</sub>Cl<sub>2</sub>/MEOH 99/1). 1.02 g (2.42 mmol, 55%) of

product were obtained as a yellow solid.

$C_{23}H_{22}N_2O_6$  (422.4); m.p. (decomp.) = 201°C;

$R_f$  = 0.5 ( $CH_2Cl_2/MeOH$  92/8).

MS (IS):  $[M+Na]^+$  = 445;  $[M-1]^-$  = 421.

Elemental analysis: calculated: C 65.40, H 5.21, N 6.64; found: C 65.37, H 5.22, N 6.67.

$^1H$  NMR ( $CDCl_3$ )  $\delta$  = 1.00-1.06 (t, 3H,  $CH_3$ ), 1.82-1.97 (m, 2H,  $CH_2$ ), 3.40 (s, 3H,  $CH_3$ ), 3.43 (s, 3H,  $CH_3$ ), 5.28-(5.33-5.72)- 5.78 (dd, 2H,  $CH_2$ ), 5.47 (s, 2H,  $CH_2$ ), 6.24 (s, 1H, CH), 7.62-7.70 (m, 2H,  $CH + CH_{Ar}$ ), 7.78-7.84 (t, 1H,  $CH_{Ar}$ ), 8.23-8.33 (m, 2H,  $CH_{Ar}$ ).

$^{13}C$  NMR ( $CDCl_3$ )  $\delta$  = 8.0; 31.9; 52.1; 52.9; 53.2; 66.7; 72.9; 98.1; 100.5; 119.0; 124.6; 125.9; 127.8; 128.4; 130.5; 138.4; 146.2; 149.4; 150.2; 152.7; 158.0; 174.1.

## PREPARATION 2

### Synthesis of intermediate product 2a

To a solution of 2.12 g (56 mmol, 3.3 eq) of  $NaBH_4$  in 70 mL of MeOH were added 7.2 g (17 mmol) of 7-dimethyl-acetal camptothecin (1a); the mixture thus obtained was stirred at ambient temperature for 1 h. At the end of this operation acetone was added to destroy the  $NaBH_4$  in excess and the solution was brought to dryness. The crude reaction product was purified by flash chromatography on silica gel (eluent gradient  $CH_2Cl_2/MeOH$  92/8  $CH_2Cl_2/MeOH$  7/3) to yield 3.7 g (8.7 mmol, 51%) of product as a yellow solid.

$C_{23}H_{24}N_2O_6$  (424.5);  $R_f$  = 0.41 (1st isomer), 0.35 (2nd isomer) ( $CH_2Cl_2/MeOH$  92/8).

MS (IS):  $[MH]^+$  = 425;  $[M+Na]^+$  = 447;  $[M-1]^-$  = 423.

Elemental analysis: calculated: C 65.09, H 5.66, N 6.60; found C 65.12, H 5.68, N 6.57.

$^1H$  NMR ( $DMSO-d_6$ )  $\delta$  = 0.84-0.90 (t, 3H,  $CH_3$ ), 1.65-1.73 (m, 2H,  $CH_2$ ), 3.38 (s, 6H,  $CH_3$ ), 4.43-(4.50-4.57) 4.64 (dd, 2H,  $CH_2$ ), 4.98 (s, 1H, CH), 5.28 (s, 2H,  $CH_2$ ), 6.32 (s, 1H, CH), 7.38 (s, 1H, CH), 7.66-7.73 (t, 1H,  $CH_{Ar}$ ), 7.8-7.88 (t, 1H,  $CH_{Ar}$ ), 8.14-8.17 (d, 1H,  $CH_{Ar}$ ), 8.3-8.33 (d, 1H,  $CH_{Ar}$ ).

$^{13}C$  NMR ( $DMSO-d_6$ )  $\delta$  = 7.6; 32.4; 50.7; 53.1; 53.5; 58.2; 70.1; 78.3; 92.5; 96.0; 98.4; 100.3; 123.1; 124.9; 127.3; 129.4; 129.9; 137.6; 142.3; 148.3; 150.1; 153.1; 157.1.

## PREPARATION 3

### Synthesis of intermediate product 3a

To a solution of 5.52 g (13 mmol) of 2a in 100 ml of  $CH_3COOH$  were added 4.17 g of  $NaIO_4$  (19.5 mmol, 1.5 eq.). The mixture was stirred at ambient temperature for 16 h; at the end of this operation, the solution was concentrated and diluted with  $CH_2Cl_2$ , then extracted with  $NaHCO_3$  to neutral pH. The organic phase was dried on  $Na_2SO_4$  and evaporated to dryness. Purification was performed by flash chromatography on silica gel

(eluents:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  98/2). 3.58 g (8.48 mmol, 65%) of product were obtained as a yellow solid.

$\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6$  (422.4); m.p. (decomp.) = 150°C;

$R_f$  = 0.6 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5).

Elemental analysis: calculated: C 65.40, H 5.21, N 6.64; found C 65.39, H 5.23, N 6.61.

MS (IS):  $[\text{MH}]^+ = 423$ ;  $[\text{M}+\text{Na}]^+ = 445$ .

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  = 1.07-1.2 (t, 3H,  $\text{CH}_3$ ), 2.96-3.3 (m, 2H,  $\text{CH}_2$ ), 3.37 (s, 6H,  $\text{CH}_3$ ), 5.12 (s, 2H,  $\text{CH}_2$ ), 5.18 (s, 2H,  $\text{CH}_2$ ), 6.37 (s, 1H, CH), 7.38 (s, 1H, CH), 7.73-7.79 (t, 1H,  $\text{CH}_{\text{Ar}}$ ), 7.86-7.92 (t, 1H,  $\text{CH}_{\text{Ar}}$ ), 8.16-8.20 (d, 1H,  $\text{CH}_{\text{Ar}}$ ), 8.27 (s, 1H, CH), 8.33-8.37 (d, 1H,  $\text{CH}_{\text{Ar}}$ ).

## PREPARATION 4

### Synthesis of intermediate product 4a

A suspension of 7.6 g (116 mmol) of zinc in 60 ml of anhydrous (distilled)  $\text{Et}_2\text{O}$ , maintained under argon and under stirring, was activated by dropwise addition of 0.87 ml (6.8 mmol) of chlorotrimethylsilane. The suspension was stirred for 15 minutes, and then brought to reflux temperature. After removing the oil bath, 17.5 ml (118 mmol) of tert-butylbromoacetate were added dropwise at a rate such as to maintain the mixture at reflux temperature: a colourless solution was obtained. After resuming heating, the reaction was maintained at reflux temperature for 1 h; at the end of this period, a suspension of 2.3 g (5.45 mmol) of 3a in 45 ml of anhydrous (distilled) THF was added, keeping the reaction under argon. The mixture thus obtained was stirred at reflux temperature. After 1 h the mixture, which had become a yellow solution, was spent with 200 ml of saturated ammonium chloride solution and extracted with  $\text{CH}_2\text{Cl}_2$ ; the organic phase was dried on  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated and the crude product purified by flash chromatography on silica gel (eluent gradient  $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{MeOH}$  98/2). 1.6 g (3.14 mmol, 58%) of product were obtained as a yellow solid.

$\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_7$  (510.6); m.p. (decomp.) = 190°C;

$R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  98/2);  $R_f$  = 0.5 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5).

MS (IS):  $[\text{MH}]^+ = 511$ ;  $[\text{M}+\text{Na}]^+ = 533$ ;  $[\text{M}-1]^- = 509$ .

Elemental analysis: calculated: C 65.88, H 6.67, N 5.49; found C 66.00, H 6.68, N 5.47.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 0.90-0.95 (t, 3H,  $\text{CH}_3$ ), 1.38 (s, 9H, t-Bu), 1.93-2.08 (m, 2H,  $\text{CH}_2$ ), 2.8-(2.86-3.08)3.14 (dd, 2H,  $\text{CH}_2$ ), 3.4 (s, 6H,  $\text{CH}_3$ ), 5.06-(5.01-5.13)-5.17 (d, 2H,  $\text{CH}_2$ ), 5.47 (s, 2H,  $\text{CH}_2$ ), 6.24 (s, 1H, CH), 7.47 (s, 1H, CH), 7.64-7.69 (t, 1H,  $\text{CH}_{\text{Ar}}$ ), 7.79-7.84 (t, 1H,  $\text{CH}_{\text{Ar}}$ ), 8.23-8.32 (m, 2H,  $\text{CH}_{\text{Ar}}$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 8.4; 28.2; 34.8; 45.5; 52.0; 53.0; 53.1; 59.1; 82.7; 100.6; 101.0;

124.8; 125.9; 128.0; 128.2; 130.0; 130.4; 130.5; 138.6; 142.4; 148.9; 152.9; 155.2; 162.6; 172.6.

## PREPARATION 5

### Synthesis of intermediate product 5a

383 mg (0.75 mmol) of **4a** and 564 mg (1.5 mmol, 2 eq.) of PDC were suspended in 4 ml of anhydrous CH<sub>2</sub>Cl<sub>2</sub>; the mixture thus obtained was placed under stirring at ambient temperature. After 16 h the solvent was removed by evaporation and the crude product thus obtained was purified by chromatography on a silica column (eluents: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99/1) yielding 280 mg (0.55 mmol, 74%) of product.

C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>7</sub> (506.5); m.p. (decomp.) = 210°C;

R<sub>f</sub> = 0.64 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5)

MS (IS): [M+Na]<sup>+</sup> = 529; [M-1]<sup>-</sup> = 505.

Elemental analysis: calculated: C 66.40, H 5.93, N 5.53; found C 66.42, H 5.96, N 5.53.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 0.83-0.90 (t, 3H, CH<sub>3</sub>), 1.33 (s, 9H, CH<sub>3</sub>), 1.97-(2.06-2.15) 2.24 (double multiplet, 2H, CH<sub>2</sub>), 2.90-(2.95-3.00) 3.05 (dd, 2H, CH<sub>2</sub>), 3.42 (s, 6H, CH<sub>3</sub>), 5.58 (s, 2H, CH<sub>2</sub>), 6.28 (s, 1H, CH), 7.39 (s, 1H, CH), 7.68-7.76 (t, 1H, CH<sub>Ar</sub>), 7.82-7.88 (t, 1H, CH<sub>Ar</sub>), 8.23-8.27 (d, 1H, CH<sub>Ar</sub>), 8.33-8.37 (d, 1H, CH<sub>Ar</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 7.6; 28.1; 31.6; 43.8; 52.5; 53.1; 53.2; 82.2; 85.0; 93.8; 100.5; 114.3; 124.9; 126.4; 129.1; 130.5; 130.9; 139.1; 149.4; 151.8; 152.4; 156.2; 167.0; 167.4; 169.9.

## EXAMPLE 1

### {10-[{(E)-(ter-butoxyimino)methyl]-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-blquinolin-3-yl}acetic acid (ST2196)}

To a solution of 71 mg (0.14 mmol) of **5a** in 1.4 ml of CH<sub>3</sub>COOH were added 44 mg (0.35 mmol, 2.5 eq.) of tBuONH<sub>2</sub>HCl; the mixture thus obtained was stirred at 80°C and sheltered from the light for 16 h. The CH<sub>3</sub>COOH was then removed by evaporation. The crude product thus obtained, kept sheltered from the light, was purified by chromatography on a silica column (eluent gradient: CH<sub>2</sub>Cl<sub>2</sub> → CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85/15). 45 mg (0.09 mmol, 68%) of product were obtained.

C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub> (475.5); m.p. (decomp.) = 228°C;

R<sub>f</sub> = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1).

MS (IS): [MH]<sup>+</sup> = 476; [M+Na]<sup>+</sup> = 498; [M-1]<sup>-</sup> = 474.

Elemental analysis: calculated: C 65.68, H 5.26, N 8.84; found: C 65.70, H 5.29, N 8.83.

<sup>1</sup>H NMR (DMSO-d6) δ = 0.63-0.7 (t, 3H, CH<sub>3</sub>), 1.5 (s, 9H, tBu), 2.07-2.17 (m, 2H, CH<sub>2</sub>), 2.97-(3.03-3.23) 3.29 (dd, 2H, CH<sub>2</sub>), 5.36 (s, 2H, CH<sub>2</sub>), 7.64 (s, 1H, CH), 7.73-

7.79 (t, 1H, CH<sub>Ar</sub>), 7.89-7.96 (t, 1H, CH<sub>Ar</sub>), 8.16-8.20 (d, 1H, CH<sub>Ar</sub>), 8.60-8.63 (d, 1H, CH<sub>Ar</sub>), 9.30 (s, 1H, CH<sub>Ar</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 7.6; 27.8; 29.9; 31.2; 42.6; 53.1; 81.9; 85.2; 94.2; 114.2; 123.2; 125.8; 127.1; 129.0; 130.8; 130.9; 132.8; 142.2; 149.8; 151.7; 152.7; 156.2; 167.2; 170.1.

### EXAMPLE 2

(10-{(E)-[(benzyloxy)imino]methyl}-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)-acetic acid (ST2285)

To a solution of 102 mg (0.2 mmol) of 5a in 2 ml of CH<sub>3</sub>COOH were added 80 mg (0.5 mmol, 2.5 eq.) of PhCH<sub>2</sub>ONH<sub>2</sub>·HCl; the solution was stirred at 80°C and sheltered from the light for 16 h. The CH<sub>3</sub>COOH was then removed by evaporation. The crude product thus obtained, kept sheltered from the light, was purified by chromatography on a silica column (eluent gradient: CH<sub>2</sub>Cl<sub>2</sub> → CH<sub>2</sub>Cl<sub>2</sub>/MeOH 8/2). 62 mg (0.12 mmol, 61%) of product were obtained.

C<sub>29</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub> (509.5); m.p. (decomp.) = 188°C;

R<sub>f</sub> = 0.53 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1).

MS (IS): [M+Na]<sup>+</sup> = 532; [M-1]<sup>-</sup> = 508.

Elemental analysis: calculated: C 68.37, H 4.52, N 8.25; found: C 68.41, H 4.50, N 8.27.

<sup>1</sup>H NMR (DMSO-d6) δ = 0.64-0.70 (t, 3H, CH<sub>3</sub>), 2.05-2.17 (m, 2H, CH<sub>2</sub>), 2.84-(2.90-3.12) 3.18 (dd, 2H, CH<sub>2</sub>), 5.2 (s, 2H, CH<sub>2</sub>), 5.4 (s, 2H, CH<sub>2</sub>), 7.36-7.58 (m, 5H, CH<sub>Ar</sub>), 7.62 (s, 1H, CH), 7.72-7.78 (t, 1H, CH<sub>Ar</sub>), 7.85-7.90 (t, 1H, CH<sub>Ar</sub>), 8.12-8.16 (d, 1H, CH<sub>Ar</sub>), 8.54-8.58 (d, 1H, CH<sub>Ar</sub>), 9.32 (s, 1H, CH<sub>Ar</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 7.0; 30.6; 42.1; 52.6; 77.8; 84.8; 93.6; 113.5; 122.6; 125.2; 126.7; 128.2; 128.5; 128.6; 128.9; 130.2; 130.3; 131.2; 136.0; 143.2; 149.1; 151.0; 152.0; 155.6; 166.9; 169.7; 170.1.

### EXAMPLE 3

R,S-7-(1-t-butoxy)iminomethyl-homocamptothecin (ST2127);

To a solution of 510 mg (1 mmol) of 4a in 10 ml of CH<sub>3</sub>COOH were added 314 mg (2.5 mmol, 2.5 eq) of tBuO-NH<sub>2</sub>·HCl; the solution was maintained sheltered from the light at 80°C for 16 h. The CH<sub>3</sub>COOH was then removed by evaporation. The crude product thus obtained, dissolved in CH<sub>2</sub>Cl<sub>2</sub> and kept sheltered from the light, was washed with water. The organic phase was dried on Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated and the crude product purified by chromatography on a silica column, keeping it sheltered from the light (eluents: CH<sub>2</sub>Cl<sub>2</sub>/dioxane 9/1). 160 mg (0.35 mmol, 34%) of solid yellow product were obtained.

C<sub>26</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub> (461,5); m.p. (decomp.) = 284°C;

R<sub>f</sub> = 0.4 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5).

MS (IS):  $[MH]^+ = 462$ ;  $[M+Na]^+ = 484$ ;  $[M-1]^- = 460$ .

Elemental analysis: calculated: C 67.68, H 5.86, N 9.11; found: C 67.65, H 5.88, N 9.13.

$^1H$  NMR ( $CDCl_3$ )  $\delta = 0.87\text{-}1.03$  (t, 3H,  $CH_3$ ), 1.55 (s, 9H,  $CH_3$ ), 1.7-1.9 (broad, 1H, OH), 1.92-2.1 (m, 2H,  $CH_2$ ), 3.26-(3.32-3.38) 3.44 (dd, 2H,  $CH_2$ ), 5.13-(5.21-5.36) 5.44 (dd, 2H,  $CH_2$ ), 5.35-(5.41-5.62) 5.68 (dd, 2H,  $CH_2$ ), 7.43-7.50 (m, 2H, CH +  $CH_{Ar}$ ), 7.60-7.65 (t, 1H,  $CH_{Ar}$ ), 7.88-7.95 (t, 2H, CH), 8.86 (s, 1H,  $CH_{Ar}$ ).

$^{13}C$  NMR ( $CDCl_3$ )  $\delta = 8.3; 27.9; 35.8; 42.7; 53.4; 62.4; 73.9; 82; 101.1; 122.9; 123.4; 125.1; 125.5; 128.3; 130.1; 130.4; 132.5; 142.1; 144.7; 149.0; 151.6; 156.4; 160.0; 171.6$ .

#### EXAMPLE 4

##### R,S-7-benzyloxyiminomethyl-homocamptothezin (ST2143);

To a solution of 510 mg (1 mmol) of **4a** in 10 ml di  $CH_3COOH$  were added 400 mg (2.5 mmol) of  $PhCH_2ONH_2 \cdot HCl$ ; the solution was kept sheltered from the light and stirred at 80°C for 16 h. The  $CH_3COOH$  was then removed by evaporation. The crude product thus obtained was purified by chromatography on a silica column (eluents:  $CH_2Cl_2/dioxane$  9/1). 223 mg of product were obtained as a yellow solid (0.45 mmol, yield 45%).

$C_{29}H_{25}N_3O_5$  (495.5); m.p. (decomp.) = 263°C;

$R_f = 0.48$  ( $CH_2Cl_2/MeOH$  95/5).

MS (IS):  $[MH]^+ = 496$ ;  $[M+Na]^+ = 518$ ;  $[M-1]^- = 494$ .

Elemental analysis: calculated: C 70.30, H 5.05, N 8.48; found: C 70.33, H 5.09, N 8.47.

$^1H$  NMR ( $CDCl_3$ )  $\delta = 0.95\text{-}1.02$  (t, 3H,  $CH_3$ ), 1.99-2.06 (m, 2H,  $CH_2$ ), 3.04-(3.08-3.18) 3.42 (dd, 2H,  $CH_2$ ), 5.32 (s, 2H,  $CH_2$ ), 5.42-(5.44-5.63) 5.70 (dd + s, 4H,  $CH_2 + CH_2$ ), 7.33-7.56 (m, 5H,  $CH_{Ar}$ ), 7.63-7.69 (m, 2H, CH +  $CH_{Ar}$ ), 7.80-7.84 (t, 1H,  $CH_{Ar}$ ), 8.16-8.22 (m, 2H,  $CH_{Ar}$ ), 9.10 (s, 1H, CH).

$^{13}C$  NMR ( $CDCl_3$ )  $\delta = 8.4; 36.5; 42.6; 52.9; 62.2; 73.6; 78.1; 101.1; 123.0; 123.1; 125.3; 126.2; 128.3; 128.5; 128.8; 129.1; 130.3; 130.4; 131.4; 136.5; 144.0; 144.4; 149.2; 152.5; 156.4; 159.7; 172.1$ .

#### EXAMPLE 5

##### Ter-butyl ester of (3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid (ST2084)

To a solution of 1 g (2.3 mmol) of **4b** in 10 ml of anhydrous  $CH_2Cl_2$  were added 1.73 g (4.6 mmol, 2 eq.) of PDC. The mixture was stirred at ambient temperature for 16 h. At the end of this period the reaction was brought to dryness and purified by flash chromatography on a silica column (eluents:  $CH_2Cl_2/MeOH$  95/5). 726 mg (1.68 mmol, 73%) of product were obtained as a yellow solid.

$C_{25}H_{24}N_2O_5$  (432.5); m.p. (decomp.) = 190°C;

$R_f$  = 0.5 ( $CH_2Cl_2/MeOH$  95/5).

MS (IS):  $[MH]^+ = 432$ ;  $[M+Na]^+ = 455$ .

Elemental analysis: calculated: C 69.44, H 5.56, N 6.48; found: C 69.46, H 5.55, N 6.51.

$^1H$  NMR ( $CDCl_3$ )  $\delta$  = 0.83-0.88 (t, 3H,  $CH_3$ ), 1.35 (s, 9H, t-Bu), 1.95-2.27 (m(double multiplet), 2H,  $CH_2$ ), 2.91-(2.96-3.01) 3.06 (dd, 2H,  $CH_2$ ), 5.38 (s, 2H,  $CH_2$ ), 7.36 (s, 1H, CH), 7.68-7.75 (t, 1H,  $CH_{Ar}$ ), 7.83-7.90 (t, 1H,  $CH_{Ar}$ ), 7.97-8.00 (d, 1H,  $CH_{Ar}$ ), 8.22-8.25 (d, 1H,  $CH_{Ar}$ ), 8.46 (s, 1H,  $CH_{Ar}$ ).

$^{13}C$  NMR ( $CDCl_3$ )  $\delta$  = 7.5; 28.1; 31.6; 43.7; 50.6; 82.2; 85.2; 94.0; 114.3; 128.5; 128.9; 130.1; 131.2; 131.7; 149.3; 151.8; 153.0; 167.4; 170.2.

## EXAMPLE 6

### (3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid (ST2085)

110 mg (0.25 mmol) of EM 21/2 were dissolved in 1.5 ml of a 1:1 mixture of  $CH_2Cl_2/TFA$ . The mixture was stirred at ambient temperature for 16 h. The solvent was then evaporated dry to yield 94 mg of product as a yellow solid (0.25 mmol, quantitative yield).

$C_{21}H_{16}N_2O_5$  (376.4); m.p. (decomp.) = 242°C;

$R_f$  = 0.25 ( $CH_2Cl_2/MeOH$  95/5).

MS (IS):  $[MH]^+ = 377$ ;  $[M+Na]^+ = 399$ ;  $[M-1]^- = 375$ .

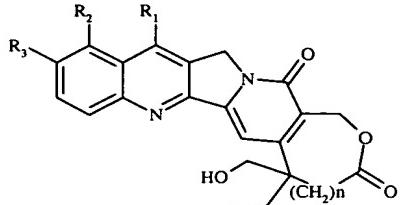
Elemental analysis: calculated: C 67.02, H 4.26, N 7.45; found C 67.05, H 4.28, N 7.49.

$^1H$  NMR ( $DMSO-d_6$ )  $\delta$  = 0.64-0.70 (t, 3H,  $CH_3$ ), 2.03-2.16 (m, 2H,  $CH_2$ ), 3.05-(3.10-3.30) 3.35 (dd, 2H,  $CH_2$ ), 4.00-4.75 (broad, 1H, OH), 5.33 (s, 2H,  $CH_2$ ), 7.65 (s, 1H, CH), 7.73-7.78 (t, 1H,  $CH_{Ar}$ ), 7.84-7.90 (t, 1H,  $CH_{Ar}$ ), 8.15-8.18 (d, 2H,  $CH_{Ar}$ ), 8.73 (d, 1H,  $CH_{Ar}$ ).

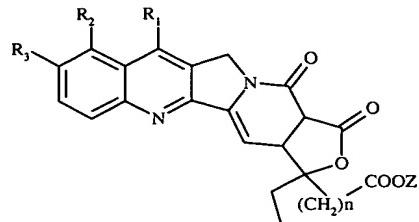
$^{13}C$  NMR ( $CDCl_3$ )  $\delta$  = 7.7; 31.2; 41.6; 51.5; 85.3; 94.5; 113.5; 129.0; 129.1; 129.4; 129.8; 131.4; 131.9; 132.6; 148.8; 152.5; 153.5; 156.0; 167.4; 170.5; 170.6.

## CLAIMS

### 1. Compounds of formula (I) or formula (II)



(I)



(II)

wherein:

R<sub>1</sub> is hydrogen or a -C(R<sub>5</sub>)=N-O-R<sub>4</sub> group, in which R<sub>4</sub> is hydrogen or a straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkenyl group, or a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, or a straight or branched (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a C<sub>6</sub>-C<sub>14</sub> aryl group, or a straight or branched (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, or a heterocyclic group or a straight or branched heterocycle - (C<sub>1</sub>-C<sub>5</sub>) alkyl group, said heterocyclic group containing at least one heteroatom selected from an atom of nitrogen, possibly substituted with an (C<sub>1</sub>-C<sub>5</sub>) alkyl group, and/or an atom of oxygen and/or of sulphur; said alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aryl-alkyl, heterocyclic or heterocycle-alkyl groups may possibly be substituted with one or more groups chosen from: halogen, hydroxy, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, phenyl, cyano, nitro, and -NR<sub>6</sub>R<sub>7</sub>, where R<sub>6</sub> and R<sub>7</sub>, which may be the same or different, are hydrogen, straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl, the -COOH group or one of its pharmaceutically acceptable esters; or the -CONR<sub>8</sub>R<sub>9</sub> group, where R<sub>8</sub> and R<sub>9</sub>, which may be the same or different, are hydrogen, straight or branched (C<sub>1</sub>-C<sub>5</sub>) alkyl; or

R<sub>4</sub> is a (C<sub>6</sub>-C<sub>10</sub>) aroyl or (C<sub>6</sub>-C<sub>10</sub>) arylsulphonyl residue, possibly substituted with one or more groups selected from: halogen, hydroxy, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl, straight or branched C<sub>1</sub>-C<sub>5</sub> alkoxy, phenyl, cyano, nitro, -NR<sub>10</sub>R<sub>11</sub>, where R<sub>10</sub> and R<sub>11</sub>, which may be the same or different, are hydrogen, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl; or:

R<sub>4</sub> is a polyaminoalkyl residue; or

R<sub>4</sub> is a glycosyl residue;

R<sub>5</sub> is hydrogen, straight or branched C<sub>1</sub>-C<sub>5</sub> alkyl, straight or branched C<sub>1</sub>-C<sub>5</sub> alkenyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, straight or branched (C<sub>3</sub>-C<sub>10</sub>) cycloalkyl - (C<sub>1</sub>-C<sub>5</sub>) alkyl, C<sub>6</sub>-C<sub>14</sub> aryl, straight or branched (C<sub>6</sub>-C<sub>14</sub>) aryl - (C<sub>1</sub>-C<sub>5</sub>) alkyl;

R<sub>2</sub> and R<sub>3</sub>, which may be the same or different, are hydrogen, oxhydryl, straight or branched C<sub>1</sub>-C<sub>5</sub> alkoxy;

n = 1 or 2,

Z is selected from hydrogen, straight or branched C<sub>1</sub>-C<sub>4</sub> alkyl;

the N<sub>1</sub>-oxides, the racemic mixtures, their individual enantiomers, their individual diastereoisomers, their mixtures, and their pharmaceutically acceptable salts, on condition that, in formula (I), R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> cannot be simultaneously hydrogen.

2. Compounds according to claim 1, in which, in formula (I), n is 1.
3. Compounds according to claim 1, in which, in formula (II), n is 1.
4. Compounds according to claim 2, selected from the group consisting of:  
R,S-7-methoxyiminomethyl-homocamptothecin;  
R,S-7-ethoxyiminomethyl-homocamptothecin;  
R,S-7-isopropoxyiminomethyl-homocamptothecin;  
R,S-7-(2-methylbutoxy)iminomethyl-homocamptothecin;  
R,S-7-(1-t-butoxy)iminomethyl-homocamptothecin;  
R,S-7-(4-hydroxybutoxy)iminomethyl-homocamptothecin;  
R,S-7-triphenylmethoxyiminomethyl-homocamptothecin;  
R,S-7-carboxymethoxyiminomethyl-homocamptothecin;  
R,S-7-aminoethoxyiminomethyl-homocamptothecin;  
R,S-7-(N,N-dimethylaminoethoxy)iminomethyl-homo- camptothecin;  
R,S-7-allyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclohexyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclohexylmethoxyiminomethyl-homocampto-thecin;  
R,S-7-cyclooctyloxyiminomethyl-homocamptothecin;  
R,S-7-cyclooctylmethoxyiminomethyl-homocamptothecin;  
R,S-7-benzyloxyiminomethyl-homocamptothecin;  
R,S-7-(benzyloxy)iminophenylmethyl-homocamptothecin;  
R,S-7-(1-benzyloxy)iminoethyl-homocamptothecin;  
R,S-7-(1-t-butoxy)iminoethyl-homocamptothecin;  
R,S-7-p-nitrobenzyloxyiminomethyl-homocamptothecin;  
R,S-7-p-metilbenzyloxyiminomethyl-homocamptothecin;  
R,S-7-pentafluorobenzyloxyiminomethyl-homocampto-theclin;  
R,S-7-p-phenylbenzyloxyiminomethyl-homocampto-theclin;  
R,S-7-(2,4-difluorobenzylmethoxy)iminomethyl-homo- camptothecin;  
R,S-7-(4-t-butylphenylmethoxy)iminomethyl-homo-camptothecin;  
R,S-7-(1-adamantyloxy)iminomethyl-homocamptothecin;

R,S-7-(1-adamantylmethoxy)iminomethyl-homocampto-theclin;  
R,S-7-(2-naphthalenyloxy)iminomethyl-homocampto-theclin;  
R,S-7-(9-anthracenylmethoxy)iminomethyl-homo-camptotheclin;  
R,S-7-(6-uracyl)methoxyiminomethyl-homocamptotheclin;  
R,S-7-(4-pyridil)methoxyiminomethyl-homocamptotheclin;  
R,S-7-(2-thienyl)methoxyiminomethyl-homocampto-theclin;  
R,S-7-[(N-methyl)-3-piperidinyl]methoxyiminomethyl-homocamptotheclin;  
R,S-7-hydroxyiminophenylmethyl-homocamptotheclin.

5. Compounds according to claim 3, selected from the group consisting of:  
(10-[(E)-(ter-butoxyimino)methyl]-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinonolin-3-yl)acetic acid  
(10-[(E)-[(benzyloxy)imino]methyl]-3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid  
(3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid  
ter-butyl ester of (3-ethyl-1,13-dioxo-11,13-dihydro-1H,3H-furo[3',4':6,7]indolizino[1,2-b]quinolin-3-yl)acetic acid.
6. Process for the preparation of formula (I) compounds according to claim 1 in which R<sub>1</sub> is hydrogen and R<sub>2</sub> and R<sub>3</sub> are as defined above, comprising:
  - a) reduction of the keto group in position 19 of the camptotheclin, possibly substituted with the envisaged meanings of R<sub>2</sub> and R<sub>3</sub>, to yield the derivative 19,20-dihydroxy;
  - b) treatment of the derivative obtained in step a) with periodate and acetic acid, to obtain the opening of the E ring;
  - c) Reformatsky reaction on the derivative obtained in step b);
  - d) formation of the E ring where n is 1 or 2.
7. Process for the preparation of formula (I) compounds according to claim 1, in which R<sub>1</sub> is a -C(R<sub>5</sub>)=N-O-R<sub>4</sub> group and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined above, comprising:
  - a) transformation of the camptotheclin, possibly substituted with the envisaged meanings of R<sub>2</sub> and R<sub>3</sub>, to 7-(di-methoxymethyl)camptotheclin;
  - b) reduction of the keto group in position 19 of the 7-(di-methoxymethyl)camptotheclin, to yield the derivative 19,20-dihydroxy;
  - c) treatment of the derivative obtained in step b) with periodate and acetic acid, to obtain the opening of the E ring;

- d) Reformatsky reaction on the derivative obtained in step c);
- e) treatment of the compound obtained in step d) with a formula  $R_4ONH_2$  oxime and simultaneous formation of ring E where n is 1 or 2.

8. Process for the preparation of formula (II) compounds according to claim 1 in which  $R_1$  is hydrogen and  $R_2$  and  $R_3$  are as defined above, comprising:

- a) reduction of the keto group in position 19 of the camptothecin, possibly substituted with the envisaged meanings of  $R_2$  and  $R_3$ , to yield the derivative 19,20-dihydroxy;
- b) treatment of the derivative obtained in step a) with periodate and acetic acid, to obtain the opening of the E ring;
- c) Reformatsky reaction on the derivative obtained in step b);
- d) treatment of the derivative obtained in step c) with PDC with formation of the E ring and, if so desired;
- e) transformation of the Z group to hydrogen.

9. Process for the preparation of formula (II) compounds according to claim 1 in which  $R_1$  is a  $-C(R_5)=N-O-R_4$  group and  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are as defined above, comprising:

- a) transformation of the camptothecin, possibly substituted with the envisaged meanings of  $R_2$  and  $R_3$ , to 7-(di-methoxymethyl)camptothecin;
- b) reduction of the keto group in position 19 of the 7-(di-methoxymethyl)camptothecin, possibly substituted with the envisaged meanings of  $R_2$  and  $R_3$ , to yield the derivative 19,20-dihydroxy;
- c) treatment of the derivative obtained in step b) with periodate and acetic acid, to obtain the opening of the E ring;
- c) Reformatsky reaction on the derivative obtained in step c);
- d) treatment of the derivative obtained in step c) with PDC with formation of the E ring;
- e) treatment of the compound obtained in step d) with a formula  $R_4ONH_2$  oxime and, if so desired,
- f) transformation of the Z group to hydrogen.

10. 7-(dimethoxymethyl)camptothecin.

11. Use of 7-(dimethoxymethyl)camptothecin as an inter-mediate product in the process according to claims 7 and 9.

12. Compounds according to any of claims 1-5 as medicines.
13. Pharmaceutical composition containing a therapeutically efficacious amount of at least one compound according to claims 1-5 in a mixture with pharmaceutically acceptable vehicles and excipients.
14. Pharmaceutical composition containing a therapeutically efficacious amount of at least one compound according to claims 1-5 in a mixture with pharmaceutically acceptable vehicles and excipients and possibly in combination with another active ingredient.
15. Pharmaceutical composition according to claim 14, in which the other active ingredient is an anticancer agent.
16. Use of a compound according to claims 1-5, for the preparation of a medicine with topoisomerase I inhibiting activity.
17. Use according to claim 16 for the preparation of a medicine useful for the treatment of tumours.
18. Use according to claim 16 for the preparation of a medicine useful for the treatment of parasitic or viral infections.

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